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Fatigue in Primary Care: Doctor, Why Am I So Tired?

Nina Mingioni, MD

Fatigue in primary care: Doctor, Why Am I So Tired?

NINA MINGIONI, MD FACP

Learning Objectives

Identify top causes of fatigue in primary care

Develop an evidence-based approach to assessing a patient with fatigue

Reflect on the evidence for available screening tools for fatigue

Doctor, why am I so tired all the time?

43-year-old woman presents to you with the chief complaint of “Doctor, I am run down all the time.”

Definition of fatigue

Multiple ones exist!

Are definitions relevant?

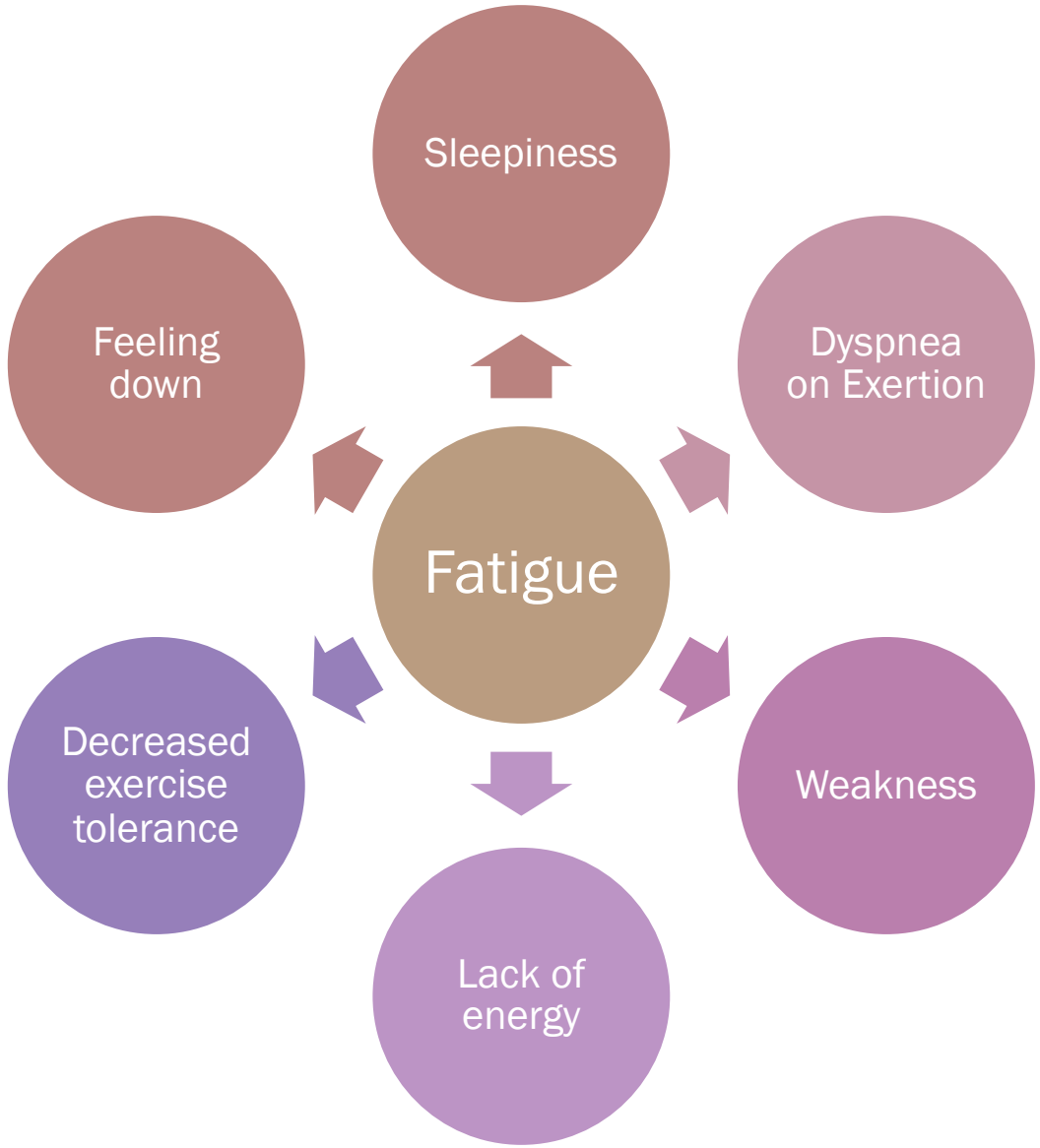
Does duration matter?

Table 1. Definitions of Fatigue.[2,7,8]

General
Progressive decline in the ability to activate the muscle voluntarily
Progressive loss of ability to generate MVC during or following repeated or sustained muscle contraction
Loss of force generation during a task
Difficulty in initiating or sustaining voluntary activity
Mismatch between expended effort and actual performance or exhaustion
Reduced force production (weakness)
Loss of exercise capacity (reduced endurance)
Increased sense of effort or overperception of force
Decreased power (reduced velocity of muscle contraction)
Loss of peak force (torque) >50%
Mental
Perception of the feeling to be cognitively fatigued after performing demanding cognitive activities that involve concentration
Central
Motor cortex failure to recruit muscle, particularly loss of high threshold motor units
Reduced central drive from increased inhibitory interneuron input to the cortex
Central conduction block from demyelination of neurons
Increased negative feedback from muscle afferents via type 3 + 4 sensory neurons
Loss of positive feedback from muscle spindle type 1 sensory afferents
Poor coordination of motor unit firing
Delayed conduction and impairment of dynamic recruitment
Changes in synergistic muscle contraction to net force
Loss of coherence between CNS motor neurons
Changes in joint mobility from spasticity
Peripheral
Progressive decline in MVC produced by a muscle
Progressive loss of MVC or decline in MVC during a task
Sense of exhaustion and lack of energy to perform repeated or sustained muscle contractions during a task
Long-lasting reduction in the activity to contract and to exert force
Incapacity to maintain the required or expected force
Diminished ATP production due to deconditioning
Disuse muscle atrophy secondary to inactivity
Muscle atrophy due to loss of innervation

Abbreviations: ATP, adenosine triphosphate; CNS, central nervous system; MVC, maximal voluntary contraction.

Finsterer J, Mahjoub SZ. Fatigue in healthy and diseased individuals. *Am J Hosp Palliat Care*. 2014;31(5):562-575.

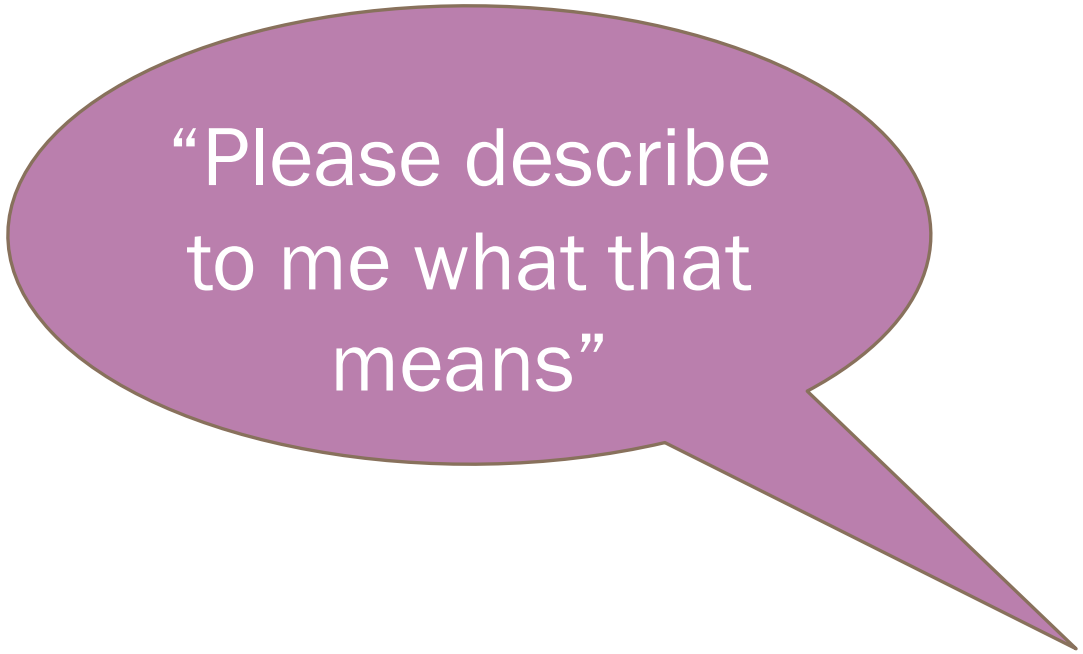

Sleepiness
Feeling down
Dyspnea on Exertion
Fatigue
Decreased exercise tolerance
Weakness
Lack of energy


Sleepiness
Feeling down
Dyspnea
n Exertion
Good history is key!
Decreased exercise tolerance
Weakness
Lack of energy

Most common (identifiable) causes of fatigue

- Anemia
- Depression
- Thyroid Disease
- Cardiopulmonary Disease
- Sleep apnea
- Side effects of medications and supplements

Start with open-ended questions…



Then explore more specifically

Start with sleep

What time do you go to sleep on a typical night?

How long does it take you to fall asleep?

Do you wake up at night? Why? How many times?

When do you wake up?

How do you feel when you wake up in the morning?

Then ask about the day

How much effort does it take to get out of bed and get moving?

Do you get sleepy throughout the day?

How likely are you to fall asleep during quiet activities, such as sitting down and reading a book or watching TV?

How is your energy level throughout the day?

How's your mood?

Assess exercise tolerance

Are you able to keep active?

What happens when you exert yourself?

Assess impact on life

What do you enjoy?

What hobbies do you have?

Have you been able to enjoy your normal day-to-day activities?

Other review of systems

- Weight changes
- Bleeding/pica
- Dyspnea
- Edema
- Bowel changes

Physical Exam

- Vital signs
- Conjunctiva
- Oropharynx
- Neck
- Cardiopulmonary exam
- Abdominal exam
- Strength testing

Mallampati Classification

Myers KA, Mrkobrada M, Simel DL. Does this patient have obstructive sleep apnea?: The Rational Clinical Examination systematic review. *JAMA*. 2013;310(7):731-741.

Also important

- Medication/supplement review
- PHQ-9

Anemia

Depression

Thyroid Disease

Cardiopulmonary Disease

Sleep apnea

Common illness scripts

Anemia: Fatigue and…

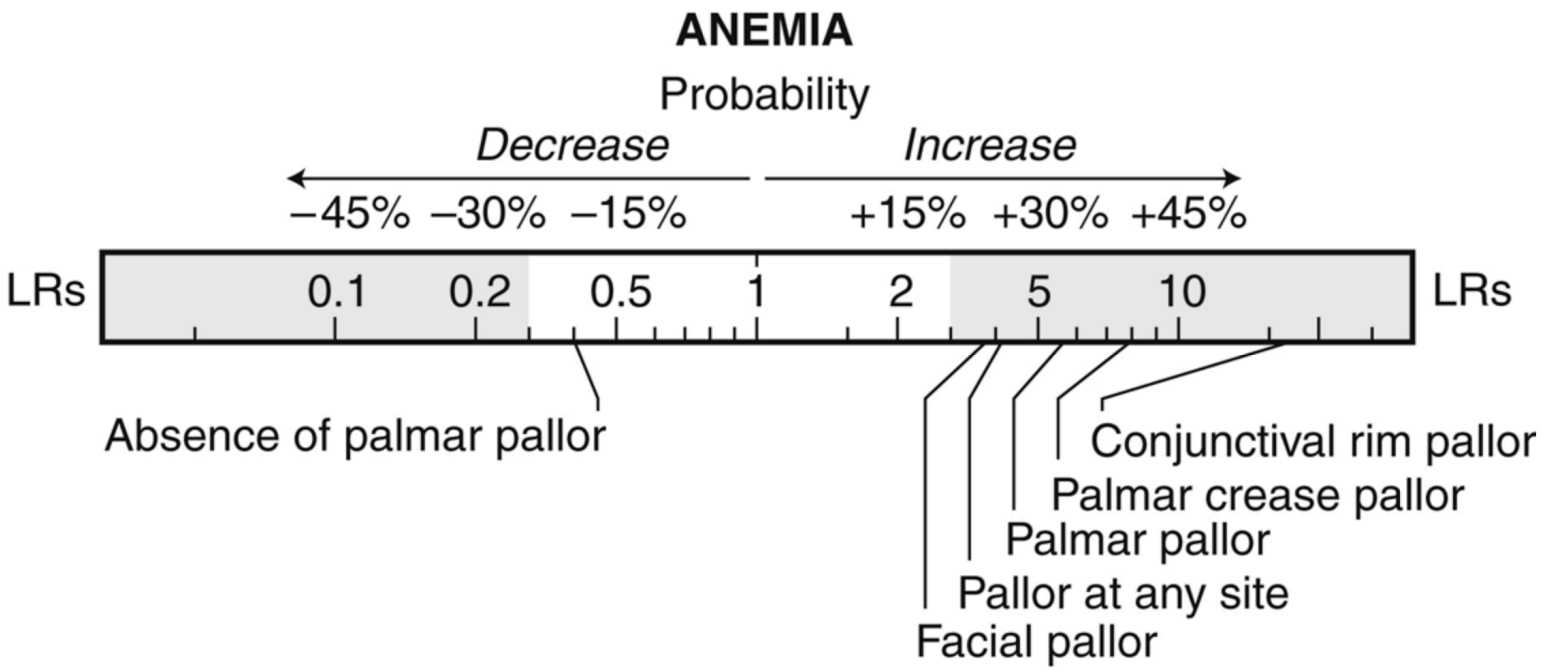
Dyspnea, dizziness, decreased exercise tolerance

May be more prevalent in younger menstruating women or those at risk for malabsorption

Pica is commonly associated (ice, clay, dirt, starch)

- Prevalence varies
- OR 2.4

Kettaneh A, Eclache V, Fain O, et al. Pica and food craving in patients with iron-deficiency anemia: a case-control study in France. *Am J Med*. 2005;118(2):185-188.
Miao D, Young SL, Golden CD. A meta-analysis of pica and micronutrient status. *Am J Hum Biol*. 2015;27(1):84-93.



McGee S. Evidence-Based Physical Diagnosis. 3rd ed. Philadelphia PA: Saunders; 2012

Sleep disorders: fatigue and…

Need for naps throughout the day

Naps improve fatigue

Sleepiness during quiet activities

Patient with obesity

DDx: Sleep apnea, insufficient sleep, sleep latency disorders

Symptom	Sensitivity	Specificity	LR+	LR-
Nocturnal choking/gasping	52%	84%	3.3	0.57
Morning headache	22%	85%	1.5	0.92
Reported apnea	80%	42%	1.4	0.47
Excessive daytime sleepiness	50%	61%	1.3	0.81
Snoring	90%	19%	1.1	0.6
Mallampati class 3 or 4	55%	65%	1.6	0.68
Overall clinical impression	58%	67%	1.7	0.67
STOP-Bang Questionnaire	93%	35%	1.4	0.2

Myers KA, Mrkobrada M, Simel DL. Does this patient have obstructive sleep apnea?: The Rational Clinical Examination systematic review. *JAMA*. 2013;310(7):731-741.

STOP-Bang Questionnaire

Please answer the following questions by checking "yes" or "no" for each one	*Yes*	*No*
Snoring (Do you snore loudly?)	❑	❑
Tiredness (Do you often feel tired, fatigued, or sleepy during the daytime?)	❑	❑
Observed Apnea (Has anyone observed that you stop breathing, or choke or gasp during your sleep?)	❑	❑
High Blood **P**ressure (Do you have or are you being treated for high blood pressure?)	❑	❑
BMI (Is your body mass index more than 35 kg per m^2?)	❑	❑
Age (Are you older than 50 years?)	❑	❑
Neck Circumference (Is your neck circumference greater than 40 cm [15.75 inches]?)	❑	❑
Gender (Are you male?)	❑	❑

Score 1 point for each positive response.

Scoring interpretation: 0 to 2 = low risk, 3 or 4 = intermediate risk, ≥ 5 = high risk.

Chung F, Yang Y, Liao P. Predictive performance of the STOP-Bang score for identifying obstructive sleep apnea in obese patients. *Obes Surg*. 2013;23(12):2050-2057.

Hypothyroidism: fatigue and…

Weight gain

Edema

Dry skin

Goiter

Family history

Finding	Sensitivity	Specificity	LR+	LR-
Cool and dry skin	16	97	4.7	0.9
Coarse skin	29-61	74-95	3.4	0.7
Periorbital puffiness	53-91	21-81	NS	0.6
Puffiness of wrists	39	86	2.9	0.7
Hair loss of eyebrows	29	85	1.9	NS
Pretibial edema	78	31	NS	NS
Hypothyroid speech	37	93	5.4	0.7
Slow pulse rate	29-43	89-98	4.2	0.7
Enlarged thyroid	46	84	2.8	0.6
Delayed ankle reflexes	48	86	3.4	0.6
Slow movements	87	13	NS	NS

McGee S. Evidence-Based Physical Diagnosis. 3rd ed. Philadelphia PA: Saunders; 2012

Cardiac disease: fatigue and…

Women are more likely than men have Acute Coronary Syndrome with no chest pain or discomfort (37% vs 27%)

Approximately 60% of all patients with Unstable Angina report unusual fatigue

Fatigue does NOT generally occur in isolation as the only symptom of ACS

- Look for associated symptoms
- Look for risk factors

Canto JG, Goldberg RJ, Hand MM, et al. Symptom presentation of women with acute coronary syndromes: myth vs reality. *Arch Intern Med*. 2007;167(22):2405-2413.

DeVon HA, Zerwic JJ. The symptoms of unstable angina: do women and men differ? *Nurs Res*. 2003;52(2):108-118.

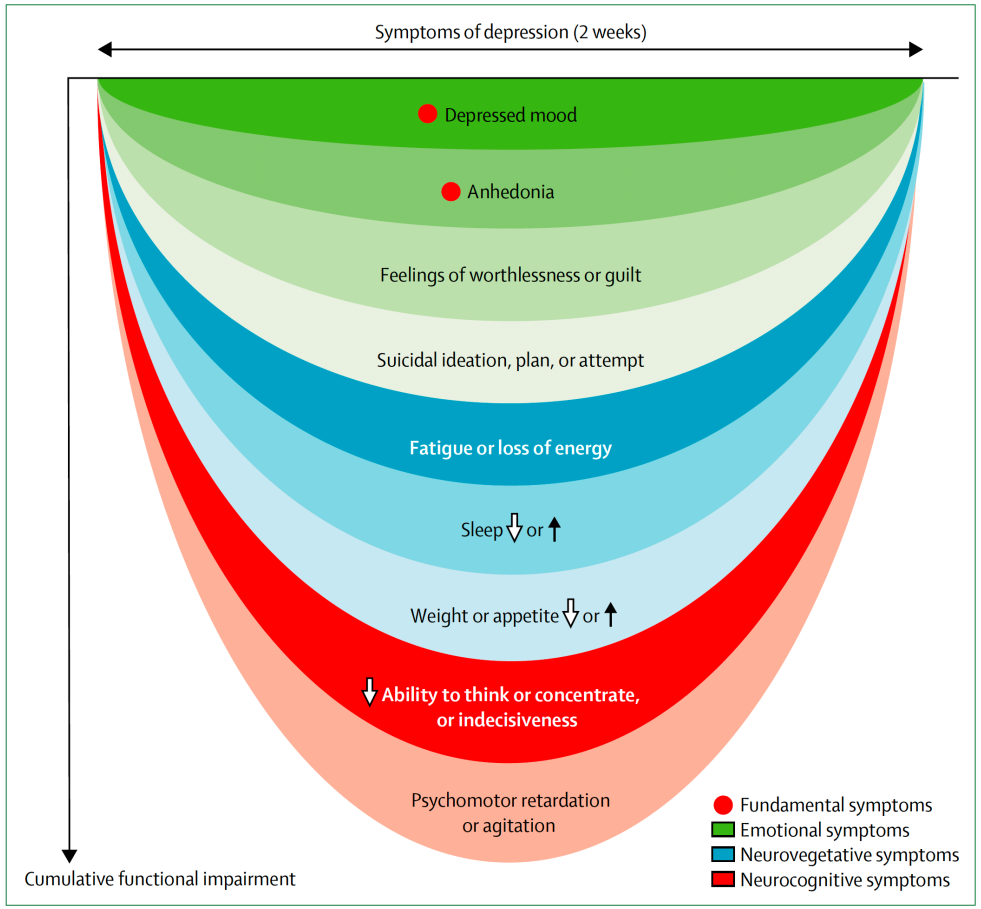
Depression: fatigue and…

Depressed mood and anhedonia are key features

At least 5 symptoms present most days for at least 2 weeks

Depressed people are twice as likely to feel fatigue and people with no depression

People with fatigue are twice as likely to also have depression as people with no fatigue



Malhi GS, Mann JJ. Depression. *Lancet*. 2018;392(10161):2299-2312.
Corfield EC, Martin NG, Nyholt DR. Co-occurrence and symptomatology of fatigue and depression. *Compr Psychiatry*. 2016;71:1-10.

PATIENT HEALTH QUESTIONNAIRE-9

Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING

0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Medications as a cause of fatigue

- Beta-blockers
- Anti-histamines
  - 1st generation
  - 2nd generation
- Narcotics
- Muscle relaxants
- Sedatives/hypnotics
- Benzodiazapines
- Gabapentin/Pregabalin
- Venlafaxine
- Tricyclic antidepressants
- Additive effects!!!

Supplements as a cause of fatigue

ST. JOHN'S WART

VALERIAN ROOT

SAW PAMETTO

OTHERS?

MEDICATION/SUPPLEMENT INTERACTION

Posadzki P, Watson LK, Ernst E. Adverse effects of herbal medicines: an overview of systematic reviews. *Clin Med* . 2013;13(1):7-12.

What if there is no clear syndrome?

Are there labs that each patient with fatigue should get?

› Am J Med Sci, 299 (5), 313-8 May 1990

The Low Yield of Physical Examinations and Laboratory Investigations of Patients With Chronic Fatigue

T J Lane [1], D A Matthews, P Manu

Affiliations + expand

PMID: 2337122 DOI: 10.1097/00000441-199005000-00005

Abstract

Fatigue is a common symptom but guidelines for its appropriate evaluation are lacking. The authors prospectively studied 100 adults with a chief complaint of fatigue lasting at least 1 month in order to determine the diagnostic contribution of physical examinations and laboratory investigations. The evaluations were performed in the specialized clinic of a faculty practice. Physical examinations produced diagnostic information in 2% of patients, and laboratory investigations elucidated the cause of fatigue in 5% of patients. Structured follow-up evaluations after an average interval of 10 months failed to reveal any new organic causes for the fatigue symptom. Minor laboratory abnormalities were relatively common but did not contribute to the diagnostic process and did not seem to influence the clinical outcome. The authors conclude that the traditional medical evaluation of patients complaining of chronic fatigue has a low yield in discovering treatable physical disorders.

Are there labs that each patient with fatigue should get?

> Fam Pract, 6 (4), 286-91 Dec 1989

Usefulness of a Standard Battery of Laboratory Tests in Investigating Chronic Fatigue in Adults

A Valdini [1], S Steinhardt, E Feldman

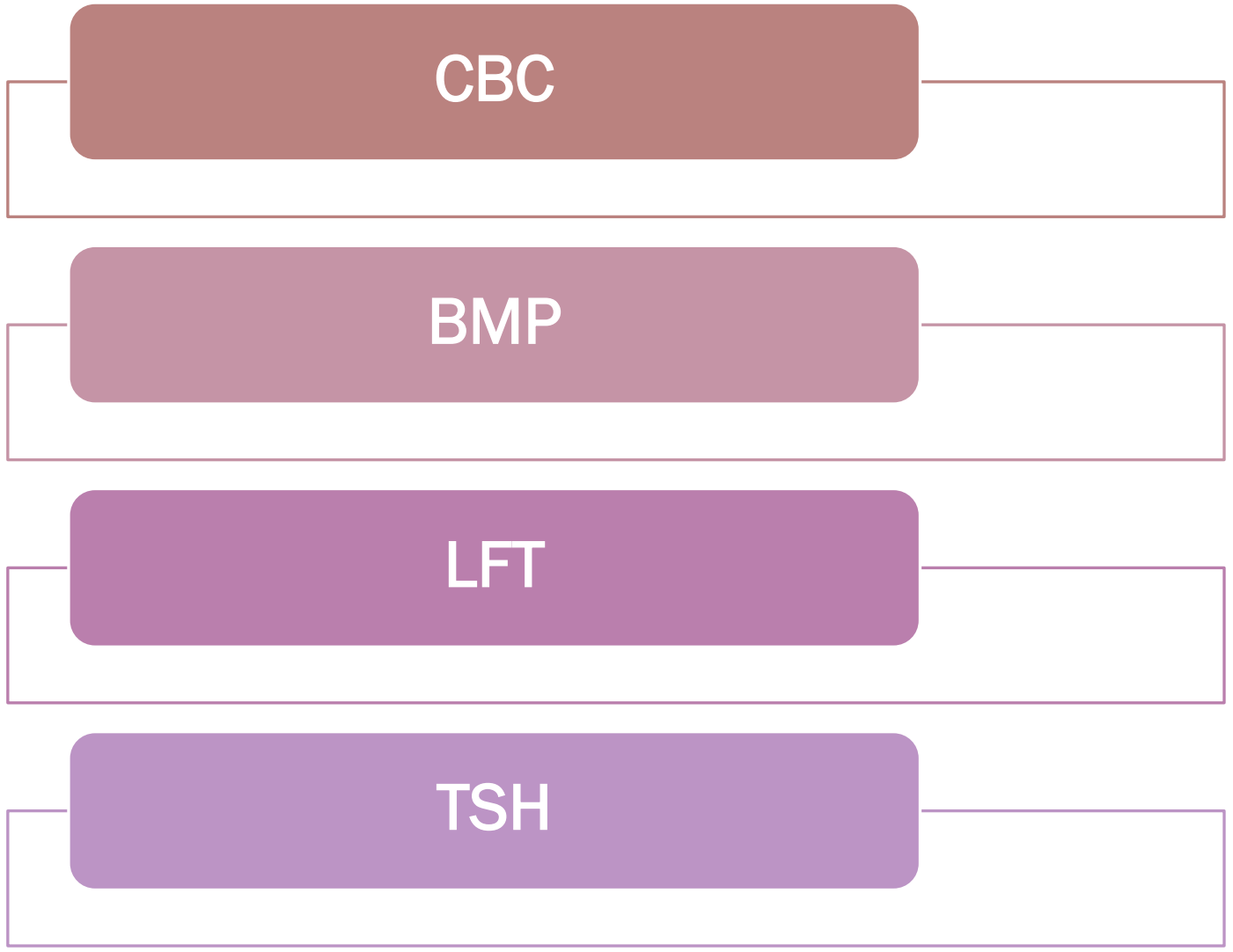
Affiliations + expand

PMID: 2632306 DOI: 10.1093/fampra/6.4.286

Abstract

Twenty-two adults with chronic fatigue were studied to determine the clinical usefulness of commonly applied laboratory tests. Subjects with the chief complaint of fatigue persisting for more than one year were followed for an average of seven months at a university family health centre. During this time a group of commonly recommended tests were carried out and the patients had repeated physical examinations. Physical diseases and laboratory abnormalities were few, and patients with abnormal values and active problems were followed until their fatigue resolved or their abnormalities reverted to normal following therapy. The study demonstrated that the presence of an abnormal laboratory result in a fatigued individual does not necessarily indicate the cause of fatigue. A psychiatric history was also performed and patients were tested with the symptom check list 90-R (SCL-90-R), a 90-item psychological symptom check list. Seven patients were receiving psychotherapy when they enrolled in the study. Two additional subjects entered therapy after the start of the study. Results on the symptom check list for the study group were largely abnormal, with a majority scoring in the highest quartile for depression, paranoid ideation and psychoticism. It is concluded that the investigation of patients with fatigue which has lasted for longer than one year should focus on psychological causes. In this group of patients laboratory abnormalities are not useful in guiding evaluation or treatment for their fatigue.

What if there is no clear syndrome



Consider Ferritin testing

In non-anemic menstruating women with unexplained fatigue and low ferritin levels iron supplementation improved fatigue.

Verdon F, Burnand B, Stubi C-LF, et al. Iron supplementation for unexplained fatigue in non-anaemic women: double blind randomised placebo controlled trial. *BMJ*. 2003;326(7399):1124.
Vaucher P, Druais P-L, Waldvogel S, Favrat B. Effect of iron supplementation on fatigue in nonanemic menstruating women with low ferritin: a randomized controlled trial. *CMAJ*. 2012;184(11):1247-1254.
Arcani R, Suchon P, Venton G, et al. Efficacy of intravenous iron therapy in non-anaemic iron-deficient patients with fatigue. *Neth J Med*. 2020;78(1):34-36.

Consider no-cost interventions

PHQ-9 Questionnaire

STOP-Bang Questionnaire

Other considerations

Make sure they are up to date on age-appropriate screening

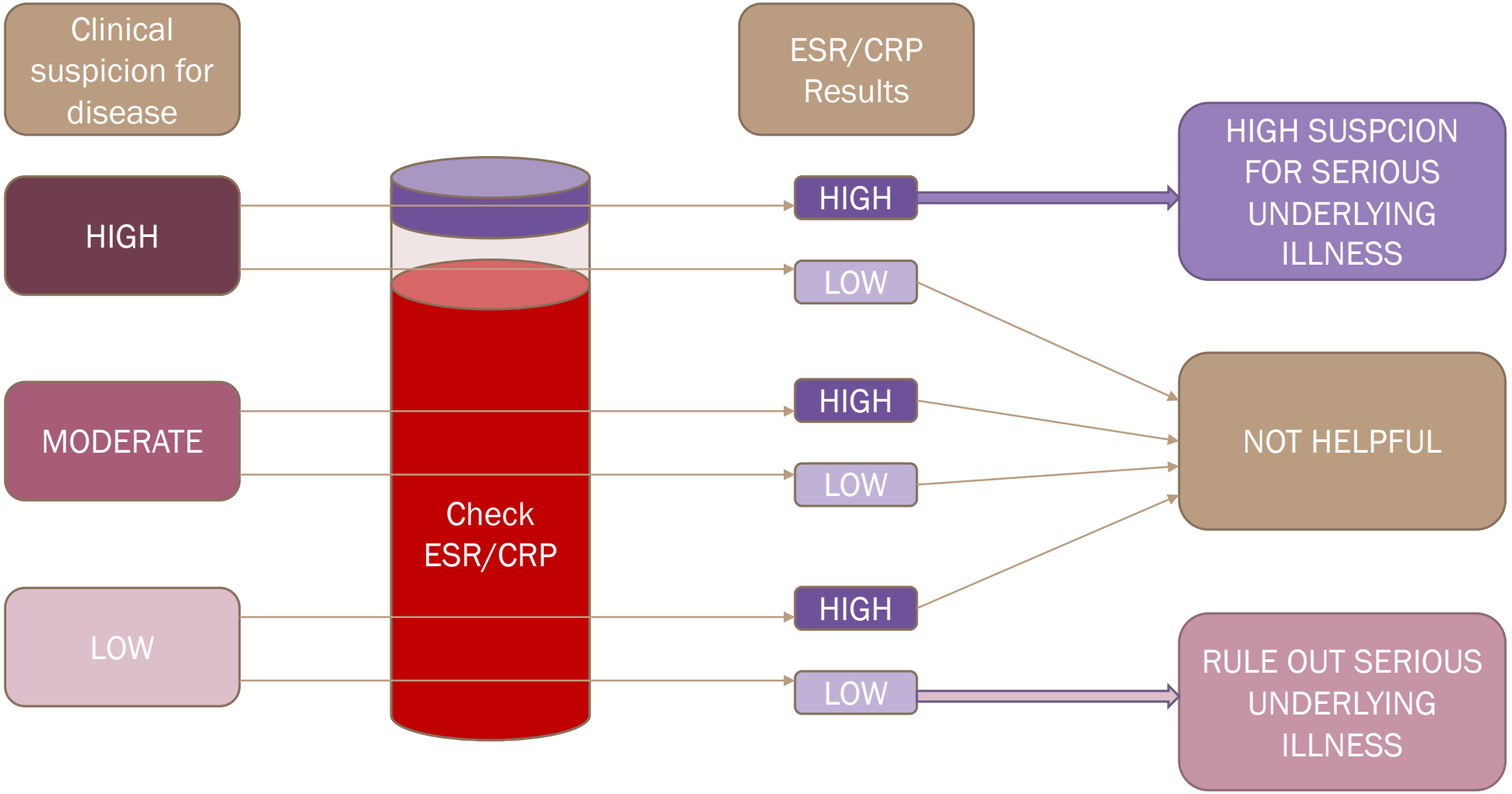
- Cancer screening
- Hepatitis C if born between 1945 and 1965
- HIV screening is recommended in all adults by USPSTF

What about other labs?

ESR/CRP

CRP	mild elevations of CRP are common
	significant elevations are consistent with bacterial infections
	drops quickly once treated
ESR	ESR>100 mm/hour: PPV>90% for an identifiable cause of marked ESR elevation
	can take weeks to return to normal

Bray C, Bell LN, Liang H, et al. Erythrocyte Sedimentation Rate and C-reactive Protein Measurements and Their Relevance in Clinical Medicine. *WMJ*. 2016;115(6):317-321.


Clinical suspicion for disease
HIGH
MODERATE
LOW
Check ESR/CRP
ESR/CRP Results
HIGH
LOW
HIGH
LOW
HIGH
LOW
HIGH SUSPCION FOR SERIOUS UNDERLYING ILLNESS
NOT HELPFUL
RULE OUT SERIOUS UNDERLYING ILLNESS

Vitamin D

Vitamin D Deficiency can be associated with:

- Muscle weakness
- Type II muscle fiber atrophy
- Accelerated sarcopenia

So:

- Might be appropriate to order if some has muscular weakness
- Not clearly associated with non-specific fatigue
- Consider screening if at risk

Vitamin B12

Vitamin B12 Deficiency:

- Neuropsychiatric symptoms WITHOUT anemia or macrocytosis (28%)
  - paresthesia, sensory loss, ataxia, dementia, and psychiatric disorders
- Macrocytosis with or without anemia
- NO isolated fatigue

Stabler SP, Allen RH, Savage DG, Lindenbaum J. Clinical spectrum and diagnosis of cobalamin deficiency. *Blood*. 1990;76(5):871-881.
Lindenbaum J, Healton EB, Savage DG, et al. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. *N Engl J Med*. 1988;318(26):1720-1728

T3 and T4

Many conditions cause decrease in total T3 and T4, but FREE T3 and T4 are relatively stable

Central hypothyroidism

- Normal TSH, low T4
- Usually due to hypopituitarism
- Symptoms can be same as primary hypothyroidism but are frequently milder due to co-existing hormonal deficiencies
- 1000 times LESS common than primary hypothyroidism

Persani L. Clinical review: Central hypothyroidism: pathogenic, diagnostic, and therapeutic challenges. *J Clin Endocrinol Metab*. 2012;97(9):3068-3078.

EBV Titers

70% of adolescents and adults with EBV infections present with Infectious Mononucleosis

90-95% of adults are eventually EBV seropositive

Association between EBV and Chronic Fatigue Syndrome is questionable

- In prospective studies, 7-13% of adults reported fatigue 6 months after an acute EBV infection.

Lennon P, Crotty M, Fenton JE. Infectious mononucleosis. *BMJ*. 2015;350:h1825.

Rheumatologic Testing

Severe fatigue is common in rheumatologic disease (35-57%)

Diagnosis of any rheumatologic disease is based on a specific syndrome alone with suggestive serologies and is never based on serology alone.

Overman CL, Kool MB, Da Silva JAP, Geenen R. The prevalence of severe fatigue in rheumatic diseases: an international study. *Clin Rheumatol*. 2016;35(2):409-415.C

Celiac Disease Testing

Celiac disease is common (1% of general population)

Fatigue is common in patients with celiac disease

- Prevalence 8-100% in various studies
- No clear evidence that fatigue improves on gluten-free diet

Patients with celiac disease usually have more than fatigue as a presenting symptom

No evidence that patients with chronic fatigue are more likely to have celiac disease

Sanders DS, Patel D, Stephenson TJ, et al. A primary care cross-sectional study of undiagnosed adult coeliac disease. *Eur J Gastroenterol Hepatol*. 2003;15(4):407-413.
Skowera A, Peakman M, Cleare A, Davies E, Deale A, Wessely S. High prevalence of serum markers of coeliac disease in patients with chronic fatigue syndrome. *J Clin Pathol*. 2001;54(4):335-336.
Skjellerudsveen BM, Omdal R, Grimstad T. Fatigue in celiac disease: A review of the literature. *JGH Open*. 2019;3(3):242-248.

Mold testing

Mold can cause legitimate medical ailments

- Allergic diseases
- Hypersensitivity pneumonitis
- Dermatologic infections
- Sepsis in immunocompromised

Toxic Mold Syndrome: fact or fiction?

- Syndrome of headache, fatigue, difficulty concentrating, myalgias, memory loss, mood changes
- Mycotoxins: no evidence, no plausible mechanism
- No FDA approved testing

Chang C, Gershwin ME. The Myth of Mycotoxins and Mold Injury. *Clin Rev Allergy Immunol*. 2019;57(3):449-455.

Lyme Titers

Untreated “stage 3” Lyme disease syndrome is oligoarthritis and neuroborreliosis

- these have defined symptoms

After treatment of Lyme disease, systemic symptoms can linger

- no evidence that indicates persistent infection
- No evidence that giving more antibiotics is helpful

“Chronic” Lyme Disease?

- Poorly defined syndrome of various atypical symptoms
- No objective clinical symptoms of recognized Lyme syndromes
- Usually negative testing

What NOT to order routinely

- Vitamin D
- Vitamin B12
- T3, T4
- Lyme testing
- EBV Titers
- Celiac panel
- Rheumatologic testing

What if no cause is found?

Does diet matter?

Maybe!

High-protein high-fat low-carb diets result in less skeletal muscle glycogen stores than high-carb diet

Depletion of muscle glycogen results in decrease in exercise tolerance.

Does my patient have occult malignancy?

No literature to support that fatigue is the only symptom of malignancy

Making sure patient is up-to-date on age-appropriate recommended cancer screening is reasonable.

Does my patient have fibromyalgia?

Diffuse pain is a central for diagnosis

Severe fatigue is common

Common co-occurrence with inflammatory conditions (central sensitization)

Does my patient have Myalgic Encephalomyelitis?

Myalgic Encephalitis/Chronic Fatigue Syndrome (ME/CFS)

Overwhelming fatigue not improved by rest

Prominent post-exertional malaise

Unrefreshing sleep

Cognitive impairment OR orthostatic intolerance

Komaroff AL. Advances in Understanding the Pathophysiology of Chronic Fatigue Syndrome. *JAMA*. July 2019. doi:10.1001/jama.2019.8312

Summary

- Good history is key!
- Illness scripts drive the work-up
- Labs: CBC, BMP, LFT, TSH
- Consider Ferritin
- Do not over-order tests
- Clinical follow up is important